Environmental Health Perspectives
Vol. 46, pp. 197-205, 1982

Mutagenic Activity Associated with By-Products of Drinking Water Disinfection by Chlorine, Chlorine Dioxide, Ozone and UV-Irradiation

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A retrospective epidemiological study in The Netherlands showed a statistical association between chlorination by-products in drinking water and cancer of the esophagus and stomach for males. A pilot-plant study with alternative disinfectants was carried out with stored water of the Rivers Rhine and Meuse. It was demonstrated that the increase of direct acting mutagens after treatment with chlorine dioxide is similar to the effect of chlorination. Ozonation of Rhine water reduced the mutagenic activity for *Salmonella typhimurium* TA 98 both with and without metabolic activation. UV alone hardly affects the mutagenicity of the stored river water for *S. typh.* TA 98. In all studies, practically no mutagenic activity for *S. typh.* TA 100 was found. Although remarkable changes in the concentration of individual organic compounds are reported, the identity of the mutagens detected is yet unclear. Compounds of possible interest due to their removal by ozonation are 1,3,3-trimethyloxindole, dicyclopentadiene and several alkylquinolines. Compounds which might be responsible for the increased mutagenicity after chlorination are two brominated acetonitriles and tri(2-chlorethyl) phosphate. Furthermore, the concentration procedure with adsorption on XAD resin and the subsequent elution step may have affected the results. It is proposed to focus further research more on the less volatile by-products of disinfection than on the trihalomethanes.

Introduction

In The Netherlands most of the drinking water does not receive a chlorine treatment. The bulk of the use of chlorine is related to surface water treatment. Even part of the drinking water derived from polluted surface water is distributed without chlorination which often is the case when bank-filtration or dune infiltration is applied. From the total chlorine consumption of 2100 tons by the waterworks of The Netherlands in 1977, 800 tons were used for raw water transport, 600 tons for break point chlorination and 700 tons for final disinfection (*1*). Since then chlorine application has been reduced as much as possible. Alternatives for chlorination which have equal oxidation or disinfection potential and which create smaller health risks are investigated by the National Institute for Water Supply (NIWS) (*2*).

The health effects of chlorination itself were studied in more detail by the NIWS. An epidemiological study was carried out, as part of a larger epidemiological study in the European Communities, under contract 273-77-1 ENV N with the Commission of the European Communities. This study is presently finalized and includes a population of 4.6 million inhabitants of the Netherlands for which cancer mortality rates for both sexes and seven cancer sites were obtained from the Central Bureau of Statistics over the years 1965–1976. The standardized mortality rates for the age group 35–64 (Table 1) showed a statistical association

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Table 1. Correlation coefficients between standard cancer mortality ratios in both sexes and drinking water quality in the Netherlands.

	Water quality aspect					
	Ground water/surface water		No chlorination/chlorination		Level of THM[a]	
Type of cancer	Male	Female	Male	Female	Male	Female
Esophagus	–0.02	0.18	0.27	0.19	0.60[b]	0.29
Stomach	0.04	–0.13	0.36	0.15	0.46[b]	0.27
Colon	–0.01	–0.12	0.00	–0.19	–0.18	–0.24
Rectum	–0.23	0.02	–0.08	0.38	–0.04	0.22
Liver	0.39[b]	0.11	0.56[b]	0.14	0.07	0.16
Bladder	0.39[b]	–0.13	0.17	–0.12	–0.03	0.03
Lung	0.53[b]	0.43	0.52[b]	0.32	0.25	–0.14

[a]r is significant ($p < 0.05$, one-tailed test).
[b]THM data obtained from a survey carried out in 1976 (*3*).

between chlorination by-products, as indicated by the trihalomethanes (THMs) and cancer of the esophagus and the stomach in males. Liver cancer and bladder cancer were not associated with chlorination by-products, although for males these cancer sites showed an association with the use of contaminated surface water as a raw water source. A further correlation study with organic micropollutants detected in drinking water derived from surface water (*3*) suggests an association between liver cancer and chlorobenzenes for males (r = 0.47), stomach and rectum cancer and alkylbenzenes for females (r = 0.57 and 0.59, respectively) and bladder cancer and phthalates for males (r = 0.39). However, as indicated by the lung cancer data, the areas supplied from contaminated surface water are situated in the most industrialized part of the country, which may confound the issue substantially (*4*).

A study of potential health hazards of alternative disinfectants for chlorine is being carried out by the National Institute for Water Supply in a small-scale pilot plant at Dordrecht as described earlier by De Greef et al. (*2*). Disinfection methods including ozone, chlorine dioxide and UV are studied in comparison with chlorine. The mutagenic activity of stored water of the Rivers Rhine and Meuse is examined after application of these agents. Furthermore, an attempt has been made to identify compounds which may be partly responsible for the mutagenicity observed in the Ames test applied. This paper presents the data obtained so far with the pilot installation.

Materials and Methods

Pilot Plant

The schematic flow diagram of the pilot plant is shown in Figure 1. Raw material is supplied to the pilot plant in a mobile zinc coated steel tank of 2 m^3 from which it is pumped at a rate of 0.270 m^3/hr into the disinfection unit which consists of two glass tube reactors. The reactors are 2 m high and each reactor has a volume of 64 liters. The residual time in the reactor is about 15 min.

Aqueous solutions of sodium hypochlorite or chlorine dioxide are dosed into the water supply line of the first reactor. Prior to the disinfectant dosing pH adjustment takes place by means of automatic dosing of hydrochloric acid or sodium hydroxide.

Ozone gas is injected through ceramic diffusers at the bottom of the reactors. Ultraviolet irradiation takes place in the sterilizer located behind the reactors. The sterilizer can be directly connected with the mobile tank by means of a bypass.

In some experiments the disinfected water was treated by direct filtration with addition of ferric chloride (10 mg Fe/l.) in a double layer filter (filtration rate of 3.5 m/hr) and by activated carbon filtration (filtration rate 9 m/hr, contact time 7 min).

Chlorine dioxide was generated by the sodium chlorine acid activation technique to minimize simultaneous formation of free chlorine (*5*). A commercially available generator (Bello-Zon, Filter GmbH, Heidelberg) to produce a stock solution of chlorine dioxide by mixing of sodium chlorite solution (7%) and hydrochloric acid (9%) was used. The concentration of free chlorine in the produced ClO_2 solution did not exceed 6%.

Ozone was produced with a Trailigaz air-fed unit, model Labo 76, with a production capacity of 3-9 g/hr.

Ultraviolet disinfection took place with a BEL-UVA-D1 unit (Berson Milieutechniek, Nuenen, The Netherlands) consisting of a stainless steel cylindrical chamber, housing a longitudinally mounted 30-watt ultraviolet lamp. The radiation intensity during the experiments was high (120 mW-sec/cm^2) at a detention time in the unit of 26 sec.

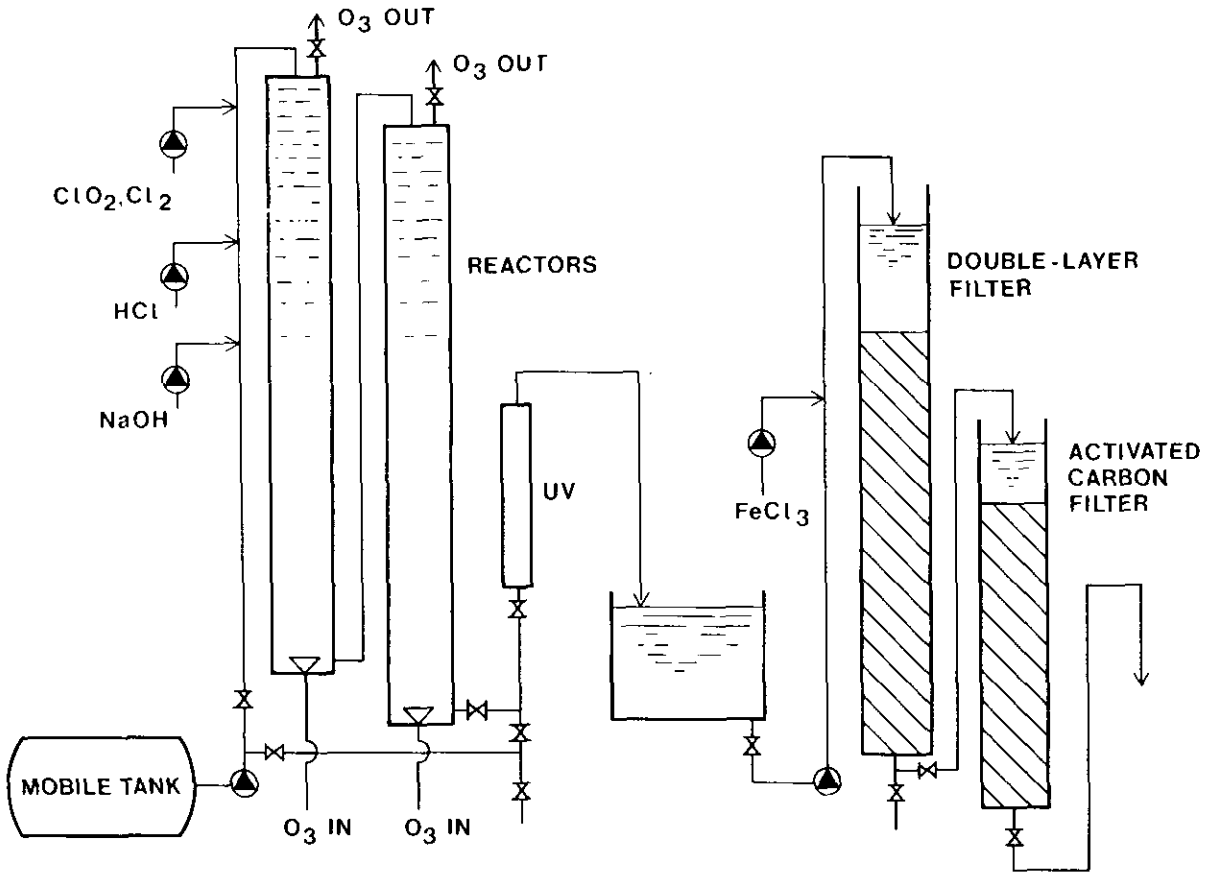

FIGURE 1. Flow diagram of the pilot plant at Dordrecht.

All experiments were monitored by standard microbiological testing for the effective removal of microorganisms. In all cases microbiological standards for drinking water were met.

Chemical Analyses

Residual concentrations of chlorine and chlorine dioxide in water were measured by the DPD-FAS technique (*6*). Chlorine, chlorine dioxide and chlorite in stock solution were determined by the iodometric method described by Berndt (*7*) and Valenta and Gabler (*8*).

Residual concentrations of ozone in water were measured iodometrically (*9*). Ozone concentration in the inlet and exhaust gas was determined iodometrically after passing a sampled gas stream through gas-washing bottles containing a 2% potassium iodide solution.

For a direct headspace analysis of very volatile halogenated compounds the procedure described by Piet et al. (*10*) was used.

Identification of organic compounds in XAD-ether concentrates was carried out according to a procedure developed by Morra et al. (*11*) using a Finnigan 4000 masspectrometer coupled with an INCOS datasystem.

Mutagenicity Testing

Mutagenicity was tested according to the method developed by Ames et al. (*12*) using *Salmonella typhimurium* (TA 98 and TA 100) with and without metabolic activation with S9–mix. The organic substances in the water had to be concentrated 2000–4000 fold from 40–80 liters of water, which was carried out by adsorption on XAD-4/8 resin followed by DMSO extraction. A volume of 0.25 ml and 0.5 ml of the DMSO concentrate was directly tested in the Ames test as described by Van Kreijl et al. (*13*) and Kool et al. (*14*) in order to obtain dose-response curves for the samples tested. In most cases no significant increases in mutagenic activity and dose response were observed with the TA 100 strain with and without metabolic activation. Therefore only the results obtained with the TA 98 strain are reported in this paper.

Results

Chlorine

According to the results of a number of chlorination experiments with stored Rhine water and stored Meuse water, chlorination tends to increase the mutagenic activity as shown in Figure 2.

Figure 2 illustrates that the effect of chlorination on the mutagenic activity depends strongly on the type of organic compounds present in the water. The increase in activity from direct acting mutagens due to chlorination is much more pronounced for Meuse water than for Rhine water. With metabolic activation chlorination of Rhine water can result in a reduction of the mutagenic activity. This is best explained by supposing that Rhine water contains more indirect mutagenic compounds than Meuse water, although other possible explanations cannot be excluded.

Due to the testing procedure applied, the volatile THMs formed by chlorination are not likely to be responsible for the mutagenicity found. The identity of the less volatile chlorination by-products which are probably responsible for the increased mutagenicity detected is yet unclear. GC-MC analysis of the XAD-ether extract containing the compounds formed resulted in the identification of a few substances, which are listed in Table 2. It should be noted that the ether-extract generally contained less mutagenic activity than the DMSO extract. Of particular interest are the two identified halogenated acetonitriles and tri(2-chloroethyl) phosphate. According to Nakamura et al. (15) the latter compound is a weak mutagen. Further studies using HPLC techniques are continuing in order to identify the compounds formed which may contribute to the increased mutagenic activity of chlorinated water.

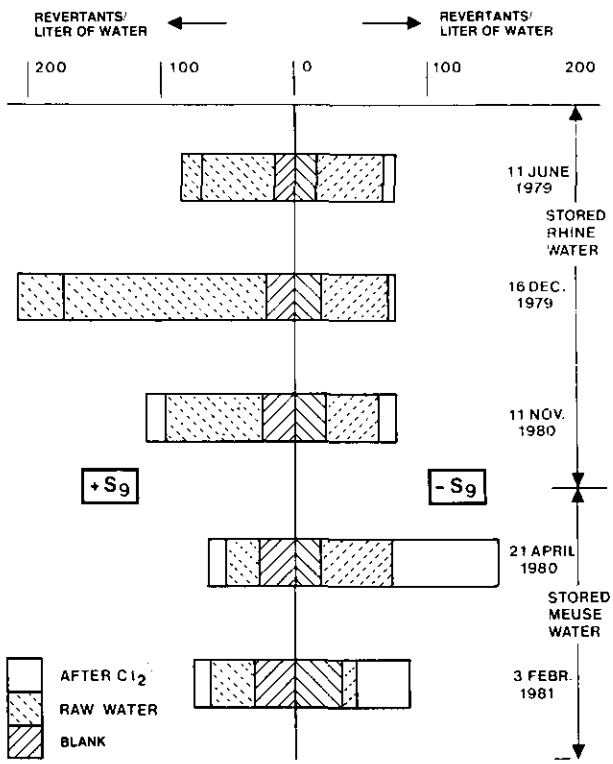

FIGURE 2. Effect of chlorination (5 mg Cl_2/l.) on mutagenicity of XAD-DMSO concentrates tested with *S. typhimurium* TA 98 (pH 8–9).

Chlorine Dioxide

Oxidation with chlorine dioxide generally resulted in a significant increase of the activity due to direct acting mutagens (Fig. 3). After metabolic activation, a considerable reduction of the mutagenic activity was observed in the case of chlorine dioxide application to Rhine water.

Table 2. Substances formed by chlorination of stored Rhine water (dose 5 mg Cl_2/l.; pH 8.1; 6.5°C).

Retention index	Compound	Concentration, µg/l. Before	After
250	Chloroform	0.1	9
370	Bromodichloromethane	0.1	35
600	Dibromochloroacetonitrile	0.5	30
675	Bromochloroacetonitrile	—[a]	3
875	Bromoform	—	6
930	Dibromoacetonitrile	—	1
1200	Acetopheone	—	1
1370	Unknown alcohol	—	1
1390	Bis(2-chloroisopropyl) ether	0.3	1
2195	Bromodichloropropane	—	0.3
2562	Unknown oxygenated compound	—	1
2670	Tri(2-chloroethyl) phosphate	1	10

[a]Denotes less than 0.1 µg/l.

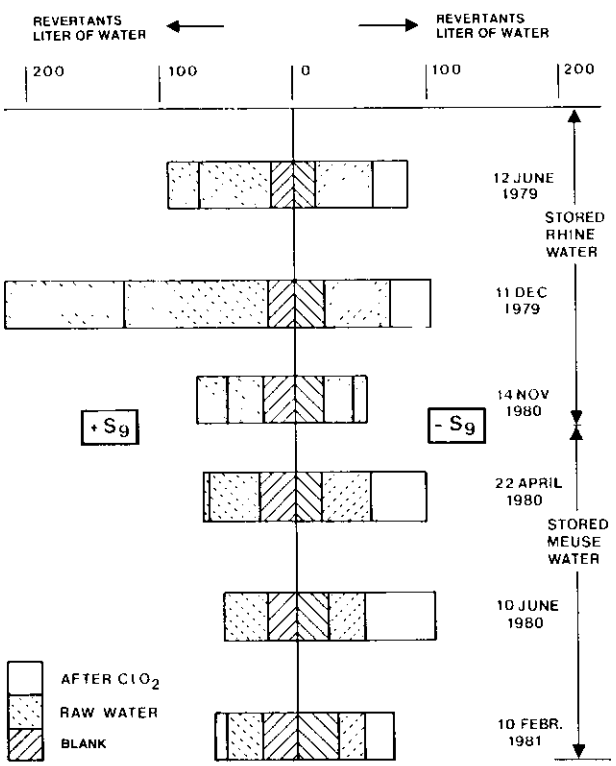

FIGURE 3. Effect of chlorine dioxide (5 mg ClO_2/l.) on mutagenicity of XAD-DMSO concentrates tested with *S. typhimurium* TA 98 (pH 8–9).

In general it seems that chlorine dioxide evoked similar or even more pronounced effects on the mutagenic activity of water than those found for chlorine. Furthermore, the effect of both oxidants is reasonably reproducible for a specific water source. During the ClO_2 experiments no important quantities of volatile halogenated compounds were formed. The THMs were generally not present at levels above 0.1 g/l. GC-MS data from previous tests (*2*) suggested that e.g. 2.6-di-*tert*-butyl-4-aminomethylphenol, 2,2,4-trimethylpenta-1,3-diol diisobutyrate and 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde are formed. The type of changes in mutagenicity indicates that the mutagenic compounds detected may be similar to those involved in chlorination processes.

Additional experiments, shown in Figure 4, indicated that the mutagenic substances originating from the raw water source or from chlorine dioxide oxidation can be effectively removed by coagulation/ filtration subsequently followed by carbon filtration.

A similar positive effect of iron coagulation on the reduction of the mutagenic activity was reported by Denkhaus et al. (*16*).

Removal of mutagens by activated carbon filtration was described also by Kool et al. (*14*) and Hrubec (*17*). However, others have found activated carbon to be inefficient in reducing mutagenic activity (*16,18,19*).

Possibly the use of "old" and "fresh" activated carbon provides an explanation for these contradictory findings.

Ozone and UV

Among the disinfectants, ozone and ultraviolet irradiation are two extremes. Ultraviolet radiation is expected to affect the identity of the organic substances only to a minor extent while ozone will oxidize organic compounds more strongly than chlorine and chlorine dioxide. In accordance with these characteristics mutagenic activity of water is unaffected by ultraviolet treatment, while the high oxidation potential of ozone results in a reduction of the mutagenicity detected in these experiments both with and without metabolic activation, as shown in Figure 5.

Similar results for ozone applied in wastewater treatment were reported by Denkhaus et al. (*16*)

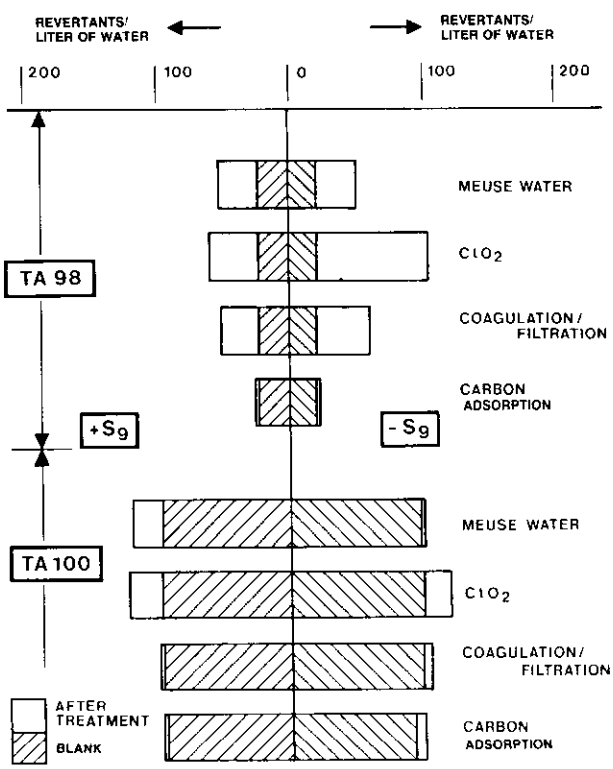

FIGURE 4. Effect of chlorine dioxide (2 mg/l.) and successive treatment by coagulation/filtration and carbon adsorption on mutagenicity of Meuse water concentrates (XAD-DMSO, *S. typhimurium* TA 98 and TA 100).

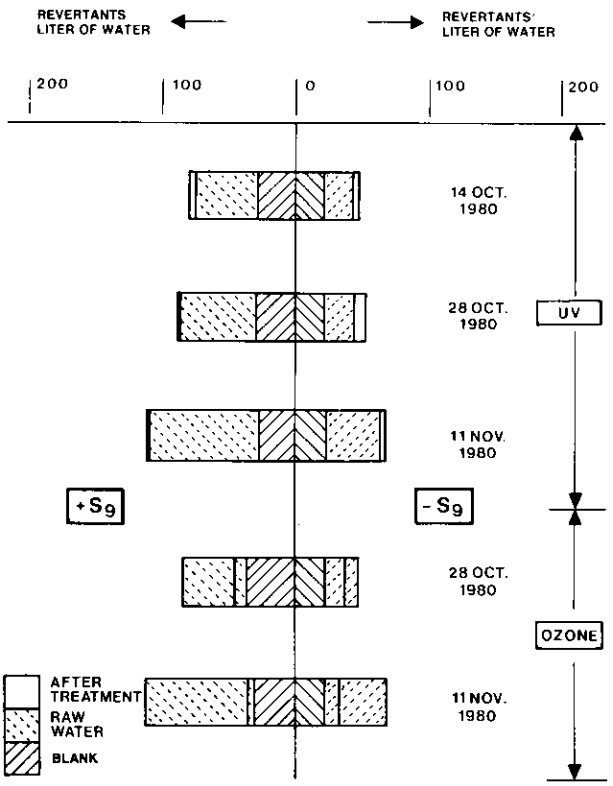

FIGURE 5. Effect of ultraviolet irradiation and ozonation on mutagenicity of stored Rhine water (XAD-DMSO, *S. typhimurium* TA 98).

and Hrubec (*17*). Also Ishizaki et al. (*20*) demonstrated detoxification of pollutants by ozonation. Indications of increases in mutagenicity after ozonation were reported by Gruener (*21*) and Simmon et al. (*22*).

GC-MS analysis of the compounds formed by ultraviolet and ozone treatment was up till now not very successful in identifying the compounds concerned. As Tables 3 and 4 indicate, oxygenated aldehydes and ketones at levels of 0.1–3 g/l. were detected in the ozonated water while the ultraviolet treatment seemed to result in the formation of benzene, toluene and compounds closely related to the substances present in the raw water, such as a dihydrotrimethylquinone isomer and a reaction product of 3,3-dimethyl-1,5-bis(isobutyl) bicyclo(3,1,0)-hexanone-2, which is presumably formed in the storage reservoir by algae.

The combination of ozone and ultraviolet irradiation was also studied.

In summary, it can be concluded that UV irradiation does not affect mutagenicity of Rhine water significantly, while ozonation reduces the mutagenic activity considerably both with and without metabolic activation. Furthermore, no formation of lower halogenated compounds was observed.

Comparison of Chlorine and Its Alternatives

The main question remaining after the discussion of the alternate disinfectants is to what extent the alternatives are better then chlorine from a health point of view. Comparative mutagenicity data for all disinfectants, including the combinations of ClO_2 with UV and O_3 with UV have been obtained for stored Rhine water and are presented in Figure 6. From these data it is clear that the mutagenicity detected of the by-products of chlorine dioxide with and without a combined ultraviolet treatment is similar to the mutagenicity detected for chlorination by-products. In this respect, the large difference in formation of trihalomethanes under these conditions seems not to be indicative for the associated health risks. However, ozone provides, at least in the case of Rhine water treatment, a better alternative to chlorine as far as the mutagenicity of the detected by-products is concerned. Both the mutagenicity of the water with and without metabolic activation is reduced. This effect is even more marked for the combination of ozone with ultraviolet irradiation. Ultraviolet treatment alone hardly affects the mutagenicity of the water.

In accordance with these observations are the GC-MS data which indicate the compounds which

Table 3. Substances formed by ozonation (8 mg/l.) of stored Rhine water.

Retention index	Compound	Concentration, μg/l.	
		Before	After
980	Heptanal	—	1
1275	Unknown oxygenated compound	—	0.1
1700	Unknown oxygenated compound	—	0.1
1750	Unknown oxygenated compound	—	0.3
2490	Unknown aldehyde	—	0.3
2555	Unknown oxygenated compound	—	1
2855	Unknown ketone	—	3

Table 4. Substances formed by ultraviolet irradiation (120 mW-sec/cm^2) of stored Rhine water.

Retention index	Compound	Concentration, µg/l. Before	After
585	Benzene	0.1	1
550	Toluene	—	3
2210	Dihydrotrimethylquinoline isomer	—	1
2320	Unknown	—	10
2515	Unknown[a]	—	1
2580	Unknown	—	1

were reduced in concentration by the alternate disinfection techniques. Table 5 illustrates that more compounds are eliminated where the more powerful oxidants are applied. Ultraviolet treatment hardly affects the concentration of the compounds identified, while ozone removes nearly all substances listed. Some of the compounds given in Table 5 such as the quinolines (*23*), might contribute to the mutagenic activity detected in Rhine water. However, the substances present in the XAD-ether concentrate can not be directly linked to the mutagenicity of the XAD-DMSO concentrates as the latter were shown to contain generally a higher mutagenic activity. Unfortunately the DMSO concentrates are not suitable for direct GC-MS analysis. A further exploration of this procedure aiming at the identification of more polar disinfection by-products is presently undertaken.

Other complications must be envisaged too. It still cannot be stated for certain whether the changes observed in mutagenic activity are really related to changes in mutagenicity of the water or if these are influenced by a different adsorption behavior of the mutagens on the XAD. The latter can result simply from the altered chemical properties of chemicals present after the disinfection treatment.

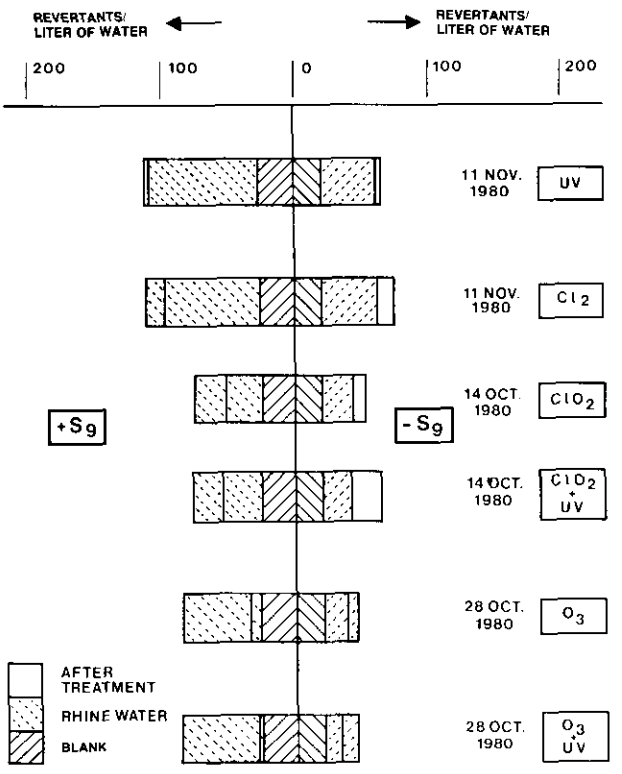

FIGURE 6. Changes in mutagenicity of stored Rhine water after disinfection by chlorine, chlorine dioxide, ozone, ultraviolet irradiation and some combinations (XAD-DMSO, *S. typhimurium* TA 98).

Table 5. Substances reduced in concentration by treatment of stored Rhine water.

Retention index	Compound	Concentration, µg/l. Raw water	After UV	After Cl_2	After O_3
1095	Unknown aldehyde/ketone	0.3	0.3	—	—
1185	Phosphoric thioic acid O,O,O-trimethyl ester	0.3	0.3	—	—
1235	Unknown aldehyde/ketone	0.3	0.3	—	—
1255	C_3-Benzene	0.1	0.1	—	—
2120	1,3,3-Trimethyloxindole	0.3	0.3	0.3	—
2155	Dicyclopentadiene	1	1	—	—
2180	Dimethylquinoline	3	3	3	—
2190	Dihydrotrimethylquinoline	10	3	—	—
2245	2,6-Bis(*tert*-butyl) 2,5-cyclohexadiene-1,4-dione	1	1	1	—
2265	3,3-Dimethyl-1,5 bis(isobutyl)bicyclo(3,1,0)hexanone-2	30	10	30	—
2438	2-(Methylthio)benzothiazole	1	1	—	—
2480	Trimethylquinoline	10	3	10	—
2650	Unknown alkylphenol	0.1	0.1	0.1	—
3010	Unknown chlorinated compound	3	3	3	0.1

[a]Denotes less than 0.1 (µg/l.)

The uncertainty this problem places on the Ames test results discussed has yet to be resolved.

Final Considerations

A retrospective epidemiological study among 1/3 of the population of The Netherlands showed a statistical association between chlorination by-products in drinking water and cancer of the esophagus and the stomach for males. An association with bladder cancer, as reported in the U.S. (*24*), was not found. Further indications were obtained that carcinogenic effects attributed to chlorination of surface water may in fact be partly due to carcinogens already present in the raw water.

The data presented suggest that a complex mixture of mutagens/carcinogens is involved. This means that generalizations of specific test results should be regarded with a certain degree of skepticism. It is against this background that the following conclusions and recommendations must be understood.

The increase of direct acting mutagens after treatment of stored river water with chlorine dioxide is similar to the mutagenic effect demonstrated after chlorination.

Ozone was found in these tests with Rhine water to reduce mutagenic activity both with and without metabolic activation.

Ultraviolet irradiation alone does not considerably influence the mutagenicity of contaminated water but it seems to enhance the diverging effects on the mutagenicity of chlorine dioxide and ozone.

An increase of mutagenicity after disinfection of the water studied for the *Salmonella typhimurium* TA 98 strain is always more pronounced without metabolic activation than with metabolic activation. In the case of Rhine water, chemical oxidation generally resulted in a decrease of the mutagenic activity (TA 98) after metabolic activation. This effect was more pronounced for $O_3 + UV > O_3 > ClO_2 + UV > ClO_2 > Cl_2 > UV$.

In all experiments practically no mutagenic activity for the *Salmonella typhimurium* TA 100 strain was demonstrated.

Although substantial differences in mutagenicity due to alternate disinfection techniques were detected, the identity of the causative mutagens is yet unclear.

The procedure applied for concentration and determination of the mutagenicity of water contaminants mainly detects the less volatile compounds. Furthermore the adsorption behavior of the mutagens on XAD is not sufficiently known. Yet, from a practical point of view, it seems justifiable from the data presented, to conclude that research in this area should focus more on the less volatile disinfection by-products than on the widely studied trihalomethanes.

Finally, within the context of the present results it may be concluded that oxidation and disinfection at the treatment station can most safely be achieved by ozonation, possibly in combination with ultraviolet irradiation. However, this leaves in many cases the problem of maintaining sufficient disinfectant residual in the water during distribution. Where this is needed, effective precursor removal, e.g., by coagulation and carbon adsorption, and a subsequent minimal safety disinfection is recommended. The data obtained so far have not indicated a substantial advantage of chlorine dioxide over chlorine for final safety disinfection.

The authors wish to thank Messrs. A. den Boer, M. J. Hart, H. J. van Kranen, C. F. van Kreijl, H. A. M. de Kruijf and P. Marsman for their valuable contribution to this study and their critical remarks in the preparation of this paper.

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